REMARKS

Amendments

Claim 10 is amended herein to recite "non-human CDR amino acid residues which bind an antigen," responsive to the Examiner's objection to the expression "non-human CDR incorporated into a human antibody."

Due to the Examiner's objection to the "improvement" language in claim 10, the phrase "wherein the improvement comprises substituting an amino acid residue for the human residue," has been replaced by "and further comprising a Framework Region (FR) amino acid substitution." (The added phrase recites "Framework Region (FR)" to provide antecedent basis for FR in claim 12.)

FR sites 63L, 67H, 91H and 103H have been deleted from claim 10 due to the overlap with FR substitutions in the humanized anti-Tac antibody of PDL's 2/13/89 priority application as discussed below. In addition, 58H and 60H are deleted since they fall within Kabat's CDR H2.

Finally, the recitation "utilizing the numbering system set forth in Kabat" is included in claim 10 to clarify the residue numbering system used in the claim. See, page 13, line 33 through to line 22 on page 14.

In that the amendments do not introduce new matter, entry thereof is respectfully requested.

Information Disclosure Statement

The Examiner states that the IDS filed 11/02/00 has been partially considered with regard to all US patents and the WO99/60023 document, but "all other documents were not considered because they were not found in the 08/146,206 application." Copies of the documents have been requested.

First, Applicants point out that all of the cited publications marked with an (*) on the 11/02/00 IDS were indeed provided to the PTO (and confirmed received thereby) with regard to the parent application (USSN

08/146,206). Nevertheless, to assist the Examiner, courtesy copies of each of the documents are being hand carried to the Examiner under separate cover. Consideration of all the art cited is respectfully requested.

A related case statement is attached. Applicants request that the Examiner consider the co-pending related applications with regard to the prosecution of the present application.

Specification

Responsive to the Examiner's objection in item 4 on page 2 of the above Office Action, the instant application is indicated, as amended, to be a "continuation" of USSN 08/146,206. Reconsideration and withdrawal of the objection is requested.

Section 112, 2nd paragraph

Claims 10-12 are rejected as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The various bases of the rejection are addressed separately below.

A. The Examiner objects to the term "improvement" in claim 10. This objection is moot in view of the amendment of claim 10 herein to remove the offending term.

B. The exact meaning of the phrase "non-human CDR incorporated into a human antibody" is considered by the Examiner to be unclear.

The rejection is moot in view of the amendment of claim 10 to recite "non-human CDR amino acid residues which bind an antigen." The specification provides guidance on the identification of CDR amino acid residues which bind an antigen and incorporation of those residues into a human antibody variable domain (see, *e.g.*, page 5, lines 30-33; page 10, lines 30-31; page 12, lines 1-9 and 13-25; page 13, lines 26-32; page 14, lines 23-28; and paragraph bridging pages 26-27, *etc*).

C. The Examiner contends that the exact meaning of the phrase "substituting an amino acid residue for the human residue" in claim 10 in not clear.

Applicants submit that the recitation (which is now reworded as "further comprising a Framework Region (FR) amino acid substitution," due to the removal of the improvement language) is clear. The specification guides the reader as to substituting a human FR residue with another residue which is preferably, but is not necessarily, found at the corresponding location of the non-human antibody. See, *e.g.* page 7, lines 30-33.

D. The recitation "no human FR residue other than those set forth in the group has been substituted" is considered by the Examiner to be indefinite.

Applicants submit that this clearly refers to the humanized antibody variable domain in which all of its FR substitution(s) - one or more FR substitutions - are selected from the Markush group of claim 10.

Reconsideration and withdrawal of the rejections is respectfully requested.

Section 112, 1st paragraph

Claims 10-12 are rejected under 35 USC Section 112, first paragraph. The Examiner contends that while the specification is enabled for a humanized antibody wherein the antibody comprises six CDRs from MAb4D5 antibody in a human framework where the antibody binds antigen, wherein the antibody comprises FR residues substituted at the recited positions from the Mab4D5 antibody, it allegedly does not provide enablement for any humanized antibody with the recited substituted residues or any antibody not having a full set of six CDRs from a non-human antibody or substituting any residues at the recited positions or humanized antibodies which do bind any antigen.

Applicants submit that the invention set forth in claim 10 and its

dependent claims is enabled by the present application. According to claim 10, non-human CDR amino acid residues which bind an antigen are incorporated into a human antibody variable domain, and the specification provides detailed guidance in this regard. See, *e.g.* page 5, lines 30-33; page 10, lines 30-31; page 12, lines 1-9 and 13-25; page 13, lines 26-32; page 14, lines 23-28; and paragraph bridging pages 26-27, *etc.* Moreover, one or more FR amino acid residue(s) are substituted as described on pages 12-13, for instance. According to claim 10, at least one of the substituted FR residues is at a site as listed in the Markush group of that claim. The teachings in the specification are clearly generalized and not limited to the MAb4D5 working example. Hence, Applicants submit that the invention set forth in claim 10 and its dependent claims is enabled.

Reconsideration and withdrawal of the Section 112, first paragraph rejection is respectfully requested.

Priority

The Examiner states that USSN 07/715,272 is not available for inspection, and in view of that, claims 10-12 in the instant application are granted the priority of 6/5/1992. Applicants attach a copy of USSN 07/715,272 filed 6/14/1991, and submit that the priority date of claims 10-12 of the instant application is 6/14/1991.

Obviousness-type double patenting

Claims 10-12 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 43-105, and 115-131 of co-pending USSN 08/146,206.

Due to the provisional nature of this rejection, Applicants ask that it be held in abeyance pending a determination that the present claims are otherwise allowable.

Section 103 - Hudziak & Adair

Claims 10-12 are rejected under 35 USC Section 103(a) as being

unpatentable over Hudziak *et al.* (US Patent No. 5,772,997) in view of Adair *et al.* (WO91/09667 published 7/11/91).

Applicants respectfully request withdrawal of this rejection in view of the fact that the priority date of claims 10-12 of the instant application is 6/14/1991 as established above. Since the priority date of claims 10-12 herein pre-dates the publication date of WO91/09667, this rejection is moot.

Section 103 - Hudziak and Queen

Claims 10-12 are rejected under 35 USC Section 103(a) as being unpatentable over Hudziak *et al.* in view of Queen *et al.* (US Patent No. 5,693,762). The Examiner contends that Queen *et al.* has "priority to at least 2/13/89" and teaches "specific residues in the FR to substitute (see Table 1)."

Applicants attach a copy of PDL's 2/13/89 priority application, which demonstrates that the specific residues listed in Table 1 of the issued '762 patent relied on by the Examiner were not described therein. The 2/13/89 priority application only describes the humanized anti-Tac antibody which had the following FR substitutions in the heavy chain variable domain 27H (27H), 30H (30H), 48H (48H), 67H (66H), 68H (67H), 93H (89H), 95H (91H), 98H (94H), 107H (103H), 108H (104H), 109H (105H), 111H (107H) and the following FR substitutions in the light chain variable domain 48L (48L), 60L (60L), and 63L (63L)[1]. Applicants have deleted the overlapping FR residues (63L, 67H, 91H and 103H) as well as 58H and 60H (which are Kabat's CDR H2 residues), from claim 10 herein, thus obviating this basis of the rejection (in terms of the relied-upon disclosure in the '762 patent lacking support in its 2/13/89 priority application).

[1]Since PDL's 2/13/89 priority application uses sequential numbering of the variable domain residues, Applicants have included the "Kabat" numbering of the residues in parentheses herein.

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Reconsideration and withdrawal of the Section 103 rejection is respectfully requested.

Respectfully submitted,

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Date: March 18, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Please amend the paragraph beginning page 1, line 5, as follows:
This is a [divisional] continuation of USSN 08/146,206 filed November 17, 1993 which is a 371 of PCT/US92/05126 filed June 15, 1992 which is a CIP of 07/715,272 filed June 14, 1991 (abandoned), the disclosures of which are incorporated herein by reference.

IN THE CLAIMS:
Please amend claim 10 as follows:
10. (Amended) A humanized antibody variable domain comprising [having a] non-human CDR amino acid residues which bind an antigen incorporated into a human antibody variable domain, [wherein the improvement comprises substituting an amino acid residue for the human residue] and further comprising a Framework Region (FR) amino acid substitution at a site selected from the group consisting of:
4L, 35L, 36L, 38L, 43L, 44L, 46L, 58L, 62L, [63L,] 64L, 65L, 66L, 67L, 68L, 69L, 70L, 71L, 73L, 85L, 87L, 98L, 2H, 4H, 24H, 36H, 37H, 39H, 43H, 45H, 49H, [58H, 60H, 67H,] 68H, 69H, 70H, 73H, 74H, 75H, 76H, 78H, [91H,] 92H, and 93H [, and 103H], utilizing the numbering system set forth in Kabat.